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(54) Title: SULFATE SALT OF A THIAZOLIDINEDIONE DERIVATIVE

(57) Abstract: A 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, a process for preparing such a salt, a pharmaceutical composition containing such a salt and the use of such a salt in medicine.

SULFATE SALT OF A THIAZOLIDINEDIONE DERIVATIVE

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

EP-A-0 306 228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of Example 30 of EP-A-0 306 228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino) ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter referred to as "Compound (I)").

WO 94/05659 discloses certain salts of the compounds of EP-A-0 306 228. The preferred salt of WO 94/05659 is the maleic acid salt. Sulfuric acid is mentioned as a favoured, pharmaceutically acceptable acid source of a potential counter-ion for salt formation. The preparation of a sulfuric acid salt is not exemplified.

There remains a need for alternative salt forms which have properties suitable for pharmaceutical processing on a commercial scale.

We have now prepared and characterised a sulfate salt of Compound (I) and discovered that a novel form of sulfate salt (hereinafter also referred as the "Sulfate") is formed that is particularly stable and hence is suitable for bulk preparation and handling.

The Sulfate is indicated to be a stable, high melting crystalline material hence is suitable for bulk preparation and handling. The Sulfate is amenable to large scale pharmaceutical processing, especially in manufacturing processes which require or generate heat, for example milling, fluid bed drying, spray drying, hot melt processing and sterilisation by autoclaving.The novel salt can be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation.

The Sulfate also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides a 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, or a solvate thereof, as a novel compound.

The Sulfate is formed from two molecules of Compound (I) and one molecule of sulfuric acid. The Sulfate consists of two molecules of Compound (I) in an appropriate ionic form and one sulfate anion. An appropriate ionic form is a protonated form. An appropriate ionic form is a cationic form. Thus the Sulfate is a 2:1 salt of Compound (I), generally in anionic form, and the SO_4^{2-} ion. The sulfate is therefore conveniently represented by the formula M_2S wherein M is a cationic form of Compound (I) and S is a sulfate anion (SO_4^{2-}).

However, a mixed (1:1) sulfate salt of Compound (I) and the SO_4^{2-} ion where the second cation is an alternative cation such as an alkali metal or ammonium cation, forms another aspect of the invention. That is a compound of formula MSN, wherein M is a cationic form of Compound (I), S is a sulfate cation (SO_4^{2-}) and N is an alternative cation such as an alkali metal or ammonium cation.

In one favoured aspect, the Sulfate provides an infrared spectrum substantially in accordance with Figure 1.

In one favoured aspect, the Sulfate provides a Raman spectrum substantially in accordance with Figure 2.

In one favoured aspect, the Sulfate provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3.

In one favoured aspect, the Sulfate provides a Solid State ^{13}C NMR spectrum substantially in accordance with Figure 4.

In a preferred aspect, the invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate, or a solvate thereof, characterised in that it provides:

(i) an infrared spectrum substantially in accordance with Figure 1; and

(ii) a Raman spectrum substantially in accordance with Figure 2; and

(iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and

(iv) a Solid State ^{13}C NMR spectrum substantially in accordance with Figure 4.

The present invention encompasses the Sulfate or a solvate thereof isolated in pure form as a mixture with other materials.

Thus in one aspect there is provided the Sulfate or a solvate thereof in isolated form.

In a further aspect there is provided the Sulfate or a solvate thereof in substantially pure form.

In yet a further aspect there is provided the Sulfate or a solvate thereof in crystalline form.

Suitably, the Sulfate melts in the range of from 183.0 to 192°C, such as 187.0 to 190.4°C or 184 - 189°C.

Moreover, the invention also provides the Sulfate, or a solvate thereof, in a pharmaceutically acceptable form, especially in bulk form, such form being particularly capable of pharmaceutical processing, especially in manufacturing processes which require or generate heat.

Examples of manufacturing processes which require or generate heat include milling, heat-drying especially fluid-bed drying, spray drying or hot melt processing and

heat-sterilisation such as autoclaving. Particular examples of manufacturing processes which require or generate heat include milling, heat-drying especially fluid-bed drying, spray drying and heat-sterilisation such as autoclaving.

Furthermore, the invention provides the Sulfate, or a solvate thereof, in a pharmaceutically acceptable form, especially in a bulk form and especially in a form having been processed in a manufacturing process requiring or generating heat, for example in a milled form; for example in a heat-dried form, especially a fluid-bed dried form; for example in a form having being hot melt processed; for example in a form having being heat-sterilised by such as autoclaving.

Suitable texts decribing the manufacturing processes referred to herein include "The Theory and Practice of Industrial Pharmacy" edited by Leon Lachman, Herbert A. Lieberman and Joseph L. Kanig, published by Lea & Febiger and for spray drying and fluid bed drying Advanced Drying Technologies by Kudra, Tadeusz.; Mujumdar, A. S, New York Marcel Dekker, Inc., 2001.

The invention also provides a process for preparing the Sulfate, or a solvate thereof, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a suitable source of sulfate ion and optionally thereafter as required:

(i) forming a solvate thereof;

(ii) recovering the Sulfate or solvate thereof ; or

(iii) further processing the Sulfate or solvate therof in a manufacturing process requiring or generating heat.

A suitable reaction solvent is an alkanol, for example methanol, or an organic acid such as acetic acid, an ester, such as ethyl acetate, an ether such as tetrahydrofuran, a nitrile such as acetonitrile, or a halogenated hydrocarbon such as dichloromethane or a hydrocarbon, such as toluene, a ketone, such as acetone, or water; or a mixture thereof.

Conveniently, the source of sulfate ion is sulfuric acid which may be concentrated sulfuric acid or may be in diluted form. The sulfuric acid may be optionally further diluted with miscible organic solvent.

For example, concentrated sulfuric acid may be added to a solution of Compound (I) in glacial acetic acid or methanol.

An alternative source of sulfate ion is provided by a base salt of sulfuric acid for example ammonium sulfate, or the sulfuric acid salt of an amine, for example ethylamine or diethylamine.

The concentration of Compound (I) is preferably in the range 3 to 50% weight/volume, more preferably in the range 5 to 20%. The concentration of sulfuric acid solutions is preferably in the range of 1 to 18 molar.

The reaction is usually carried out at ambient temperature or at an elevated temperature, for example at the reflux temperature of the solvent, although any convenient temperature that provides the required product may be employed.

As indicated above the Sulfate can exist as a solvate. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates. Thus a suitable solvate is a hydrate.

Solvates, such as hydrates, of the Sulfate may be prepared according to conventional procedures, for example by crystallising or recrystallising from a solvent which provides or contains the solvate moiety, or by exposing the Sulfate to the solvate moiety as a vapour. When the solvate is formed by crystallization methods the nature of the solvate is typically dictated by the solvent from which the Sulfate is crystallized. A Sulfate solvate is a favoured aspect of the invention.

Recovery of the required compound generally comprises crystallisation from an appropriate solvent, conveniently the reaction solvent, usually assisted by cooling. For example, the Sulfate may be crystallised from a ketone such as acetone or a hydrocarbon such as toluene. An improved yield of the salt can be obtained by evaporation of some or all of the solvent or by crystallisation at elevated temperature followed by controlled cooling. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the product form.

Crystallisation can also be initiated by seeding with crystals of the Sulfate or a solvate thereof but this is not essential.

Suitable manufacturing processes requiring or generating heat include milling, heat-drying, especially a fluid-bed drying, hot melt processing or heat-sterilisation, such as autoclaving.

Compound (I) is prepared according to known procedures, such as those disclosed in EP-A-0 306 228 and WO 94/05659. The disclosures of EP-A-0 306 228 and WO 94/05659 are incorporated herein by reference.

Sulfuric acid is a commercially available compound.

When used herein the term "T_{onset}" is generally determined by Differential Scanning Calorimetry and has a meaning generally understood in the art, as for example expressed in "Pharmaceutical Thermal Analysis, Techniques and Applications, Ford and Timmins, 1989 as "The temperature corresponding to the intersection of the pre-transition baseline with the extrapolated leading edge of the transition".

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides the Sulfate or a solvate thereof for use as an active therapeutic substance.

More particularly, the present invention provides the Sulfate or a solvate thereof for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

The Sulfate or a solvate thereof may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. Suitable methods for formulating the Sulfate or a solvate thereof are generally those disclosed for Compound (I) in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Sulfate or a solvate thereof and a pharmaceutically acceptable carrier therefor.

The Sulfate or a solvate thereof is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders,

injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulfate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised

by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Sulfate or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of Sulfate or a pharmaceutically acceptable solvate thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Sulfate or a pharmaceutically acceptable solvate thereof may be taken in amounts so as to provide Compound (I) in suitable doses, such as those disclosed in EP 0,306,228, WO94/05659 or WO98/55122.

The unit dose compositions of the invention comprise the Sulfate or a pharmaceutically acceptable solvate thereof in an amount providing up to 12 mg, including 1-12 mg such as 2-12 mg of Compound (I), especially 2-4 mg, 4-8 mg or 8-12 mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I). Thus in particular there is provided a pharmaceutical composition comprising the Sulfate or a pharmaceutically acceptable solvate thereof and a pharmaceutically acceptable carrier thereof, wherein the Sulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 1, 2, 4, 8, 12, 4 to 8 or 8 to 12 mg of Compound (I); such as 1mg of Compound (I); such as 2 mg of Compound (I); such as 4 mg of Compound (I); such as 8 mg of Compound (I); such as 12 mg of Compound (I).

The invention also provides a pharmaceutical composition comprising the Sulfate or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents and optionally a pharmaceutically acceptable carrier therefor.

The invention also provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective,

non-toxic, amount of the Sulfate or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents.

In a further aspect the present invention provides the use of the Sulfate or a pharmaceutically acceptable solvate thereof in combination with one or more other anti-diabetic agents, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the above mentioned treatments the administration of the Sulfate or a pharmaceutically acceptable solvate thereof and the other anti-diabetic agent or agents includes co-administration or sequential administration of the active agents.

Suitably in the above mentioned compositions, including unit doses, or treatments the Sulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing up to 12mg, including 1-12mg, such as 2-12mg of Compound (I), especially 2-4 mg, 4-8 mg or 8-12 mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 mg of Compound (I) or 4 to 8 or 8 to 12 mg of Compound (I). Thus for example in the above mentioned compositions, including unit doses, or treatments the Sulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 1 mg of Compound (I); the Sulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 2 mg of Compound (I); the Sulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 3 mg of Compound (I); the Sulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 4 mg of Compound (I); or the Sulfate or a pharmaceutically acceptable solvate thereof is present in an amount providing 8mg of Compound (I).

The other antidiabetic agents are suitably selected from biguanides, sulfonylureas and alpha glucosidase inhibitors. The other antidiabetic agent is suitably a biguanide. The other antidiabetic agent is suitably a sulfonylurea. The other antidiabetic agent is suitably a alpha glucosidase inhibitor. Suitable antidiabetic agents are those disclosed in WO98/57649, WO98/57634, WO98/57635, WO98/57636, WO99/03477, WO99/03476. The contents of the above mentioned publications are incorporated herein by reference as if set out in full herein.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following examples illustrate the invention but do not limit it in any way.

Example 1: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione sulfate

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (20.0 g) in glacial acetic acid (50 ml) was stirred and heated to 75°C until a clear solution was observed. Concentrated sulfuric acid (1.5 ml) was added and the stirred solution cooled to 21°C. After evaporation of solvent under reduced pressure, methanol (100 ml) was added and the mixture stirred at 21°C for 48 hours. The solid was collected by filtration, washed with methanol (50 ml) and dried under vacuum to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate (10.7 g) as a crystalline solid.

Melting point: 184 - 189°C.

DSC: T_{onset} = 184.4°C, T_{peak} = 189.1°C

Elemental Analysis:

Found:	C; 52.96	H; 4.94	N; 10.23	S; 11.78
Theory: ($C_{36}H_{40}N_6O_{10}S_3$)	C; 53.19	H; 4.96	N; 10.34	S; 11.83

Example 2: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione sulfate

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (40.0 g) in glacial acetic acid (100 ml) was stirred and heated to 70°C until a clear solution was observed. Concentrated sulfuric acid (3.1 ml) was added and the mixture stirred for 10 minutes at 70°C, then cooled to 21°C with stirring. The solvent was evaporated under reduced pressure, followed by the addition of methanol (100 ml) and the mixture was stirred at 21°C until crystallisation was complete. The product was collected by filtration, washed with methanol (200 ml) and dried under vacuum over phosphorus pentoxide for 4 hours at 50°C to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate (36.9 g) as an off white crystalline solid.

Example 3: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione sulfate

Concentrated sulfuric acid (1.94 ml) was added to a stirred suspension of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (25.0 g) in methanol (1000 ml) at 56°C. The reaction mixture was stirred at 60°C until a clear solution was observed, then cooled to 21°C and stirred at this temperature for 16 hours.

The product was collected by filtration, washed with methanol (100 ml) and dried under vacuum at 21°C for 3 hours to afford 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate (19.5 g) as a white crystalline solid.

Characterising data recorded for the product of Example 1:

The infrared absorption spectrum of a mineral oil dispersion of the product was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution (**Figure 1**). Data were digitised at 1 cm^{-1} intervals. Bands were observed at: 2925, 2853, 2656, 1740, 1696, 1644, 1609, 1545, 1511, 1460, 1420, 1377, 1331, 1302, 1259, 1248, 1236, 1167, 1087, 1028, 966, 935, 830, 821, 808, 774, 739, 718, 664, 632, 614, 603, 560, 528, 508 cm^{-1}.

The infrared spectrum of the solid product was recorded using Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a universal ATR accessory. Bands were observed at: 2917, 2644, 1741, 1689, 1643, 1607, 1544, 1510, 1480, 1461, 1440, 1419, 1392, 1369, 1330, 1303, 1258, 1247, 1236, 1167, 1066, 1028, 1004, 965, 933, 829, 820, 808, 773, 739, 717, 664 cm^{-1}.

The Raman spectrum of product (**Figure 2**) was recorded with the sample in a glass vial using a Perkin-Elmer 2000R FT-Raman spectrometer, at 4 cm^{-1} resolution with excitation from a Nd:YAG laser (1064 nm) with a power output of 400mW. Bands were observed at: 3068, 2912, 1742, 1612, 1546, 1457, 1441, 1391, 1332, 1269, 1204, 1182, 1151, 1107, 1029, 986, 937, 900, 821, 777, 745, 673, 636, 604, 511, 476, 434, 396, 350 cm^{-1}.

The X-Ray Powder Diffraction (XRPD) pattern of the product (**Figure 3**) was recorded using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator current: 40 mA, Start angle: 2.0 °2θ, End angle: 35.0 °2θ, Step size: 0.02 °2θ , Time per step: 2.5 seconds. Characteristic XRPD angles and relative intensities are recorded in Table 1.

Table 1

Angle	Rel. Intensity
2-Theta °	%
6.0	13.6
11.1	5.5
11.4	26.9

11.9	26.1
12.3	21.4
13.3	31.4
14.0	19.4
15.5	49.6
16.1	37.0
16.8	8.7
18.3	24.9
18.7	16.5
19.8	29.2
20.7	34.1
21.1	28.6
22.0	100.0
23.5	28.5
24.1	61.2
24.7	34.1
25.2	36.2
25.7	29.7
26.1	30.2
26.7	33.1
27.5	43.2
28.5	16.1
29.1	16.5
30.3	17.0
30.7	19.9
31.2	15.1
31.7	17.5
32.3	17.2
32.7	21.8
33.2	24.9

The solid-state NMR spectrum of the product (**Figure 4**) was recorded on a Bruker AMX360 instrument operating at 90.55 MHz: The solid was packed into a 4 mm zirconia MAS rotor fitted with a Kel-F cap and rotor spun at ca.10 kHz. The ^{13}C MAS spectrum was acquired by cross-polarisation from Hartmann-Hahn matched protons (CP contact time 3 ms, repetition time 15 s) and protons were decoupled during acquisition using a two-pulse phase modulated (TPPM) composite sequence. Chemical shifts were externally referenced to the carboxylate signal of glycine at 176.4 ppm relative to TMS and were observed at: 40.4, 51.7, 56.0, 58.9, 66.6, 111.2, 113.9, 117.3, 128.0, 130.1, 136.9, 138.9, 145.1, 151.6, 158.2, 172.4, 175.4, 176.6 ppm.

Properties of the Sulfate, recorded for the product of Example 3

Solid State Stability of the Sulfate

The solid state stability of the drug substance was determined by storing approximately 1.0 g of the material in a glass bottle at i) 40°C / 75% Relative Humidity (RH), open exposure, for 1 month and b) at 50°C, closed, for 1 month. The material was assayed by HPLC for final content and degradation products in both cases.

a) 40°C / 75% RH: No significant degradation observed (HPLC assay 102% initial).

b) 50°C: No significant degradation observed (HPLC assay 96% initial).

T_{onset} of the Sulfate

The T_{onset} of the drug substance was determined by Differential Scanning Calorimetry using a Perkin-Elmer DSC7 apparatus.

T_{onset} (10°C/minute, closed pan): 181.9°C

Melting Range of the Sulfate

The melting range of the Sulfate was determined according to the method described in the U.S. Pharmacopoeia, USP 23, 1995, <741> "Melting range or temperature, Procedure for Class Ia", using a Buchi 545 melting point instrument.

Melting range: 187.0 – 190.4°C

CLAIMS

1. A 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt.

2. A compound according to claim 1, characterised by an infrared spectrum substantially in accordance with Figure 1 herein (the Sulfate).

3. A compound according to claim 1, characterised by a Raman spectrum substantially in accordance with Figure 2 herein.

4. A compound according to claim 1, characterised by an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3 herein.

5. A compound according to claim 1, characterised by a Solid State ^{13}C NMR spectrum substantially in accordance with Figure 4 herein.

6. A 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, characterised by:
(i) an infrared spectrum substantially in accordance with Figure 1; and
(ii) a Raman spectrum substantially in accordance with Figure 2; and
(iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and
(iii) a Solid State ^{13}C NMR spectrum substantially in accordance with Figure 4.

7. A compound according to any one of claims 1 to 6, or a solvate thereof, in isolated form.

8. A compound according to any one of claims 1 to 6, or a solvate thereof, in substantially pure form.

9. A compound according to any one of claims 1 to 6, or a solvate thereof, in crystalline form.

10. A compound according to any one of claims 1 to 6, or a solvate thereof, in a form having been processed in a manufacturing process requiring or generating heat.

11. A compound according to claim 10, or a solvate thereof, in a bulk form.

12 A compound according to claim 10 or 11, or a solvate thereof, wherein the processed form is selected from: a milled form, a heat-dried form, a hot melt processed form and a heat-sterilised form.

13 A compound according to any one of claims 10 to 12, or a solvate thereof, in a milled form.

14. A process for preparing a compound according to any one of claims 1 to 9, or a solvate thereof, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy] benzyl]thiazolidine-2,4-dione (Compound (I))or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a source of sulfate ion; and optionally thereafter as required:
(i) forming a solvate thereof;
(ii) recovering the Sulfate or solvate thereof ; or
(iii) further processing the Sulfate or solvate therof in a manufacturing process requiring or generating heat.

15. A pharmaceutical composition comprising 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, (the Sulfate) or a pharmaceutically acceptable solvate thereof, according to claim 1, and a pharmaceutically acceptable carrier therefor.

16. A pharmaceutical composition comprising the 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, (the Sulfate) or a pharmaceutically acceptable solvate thereof, according to claim 1, in combination with one or more other anti-diabetic agents and optionally a pharmaceutically acceptable carrier therefor.

17. A pharmaceutical composition according to claim 15 or claim 16, wherein the Sulfate or the pharmaceutically acceptable solvate thereof, is present in an amount providing 1, 2, 4, 8, 12, 4 to 8 or 8 to 12 mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino) ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)).

18. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, or a pharmaceutically acceptable solvate thereof, according to claim 1, for use as an active therapeutic substance.

19. A compound 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

20. A use of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, or a pharmaceutically acceptable solvate thereof, according to claim 1, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

21. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione sulfate salt, or a pharmaceutically acceptable solvate thereof, according to claim 1, to a human or non-human mammal in need thereof.

Figure 1 Infrared spectrum of the Sulfate

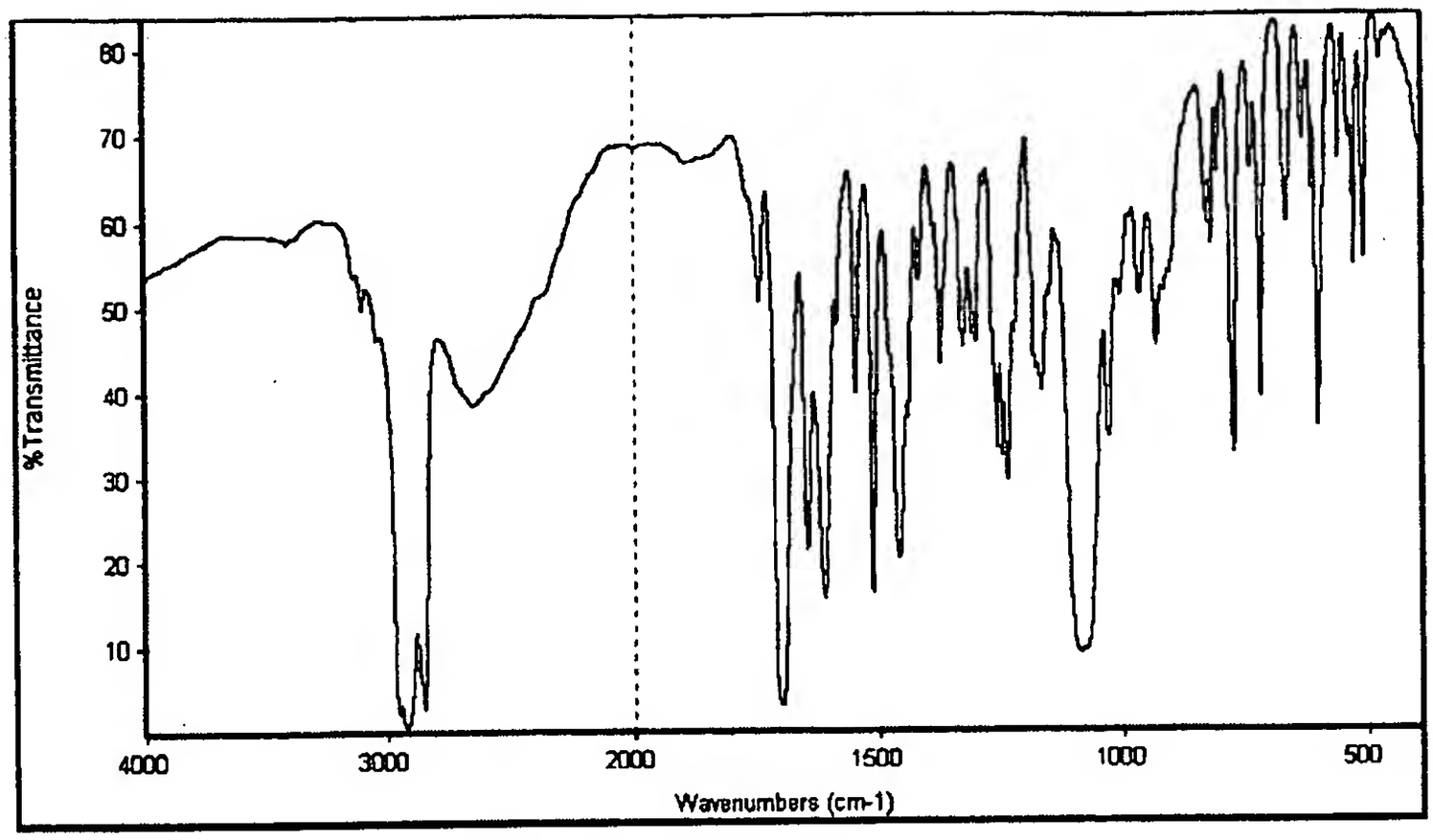


Figure 2 Raman spectrum of the Sulfate

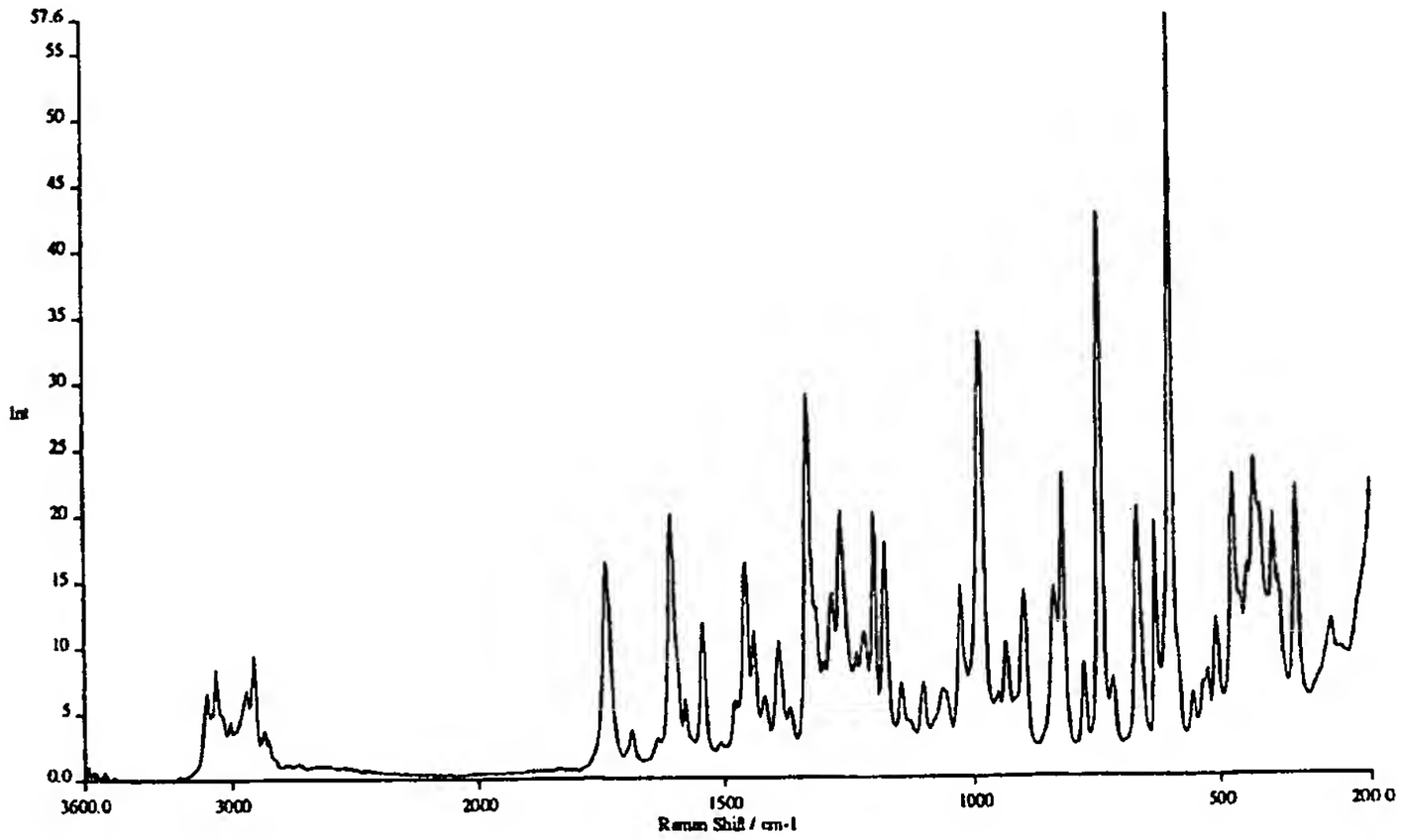


Figure 3 X-Ray Powder Diffractogram of the Sulfate

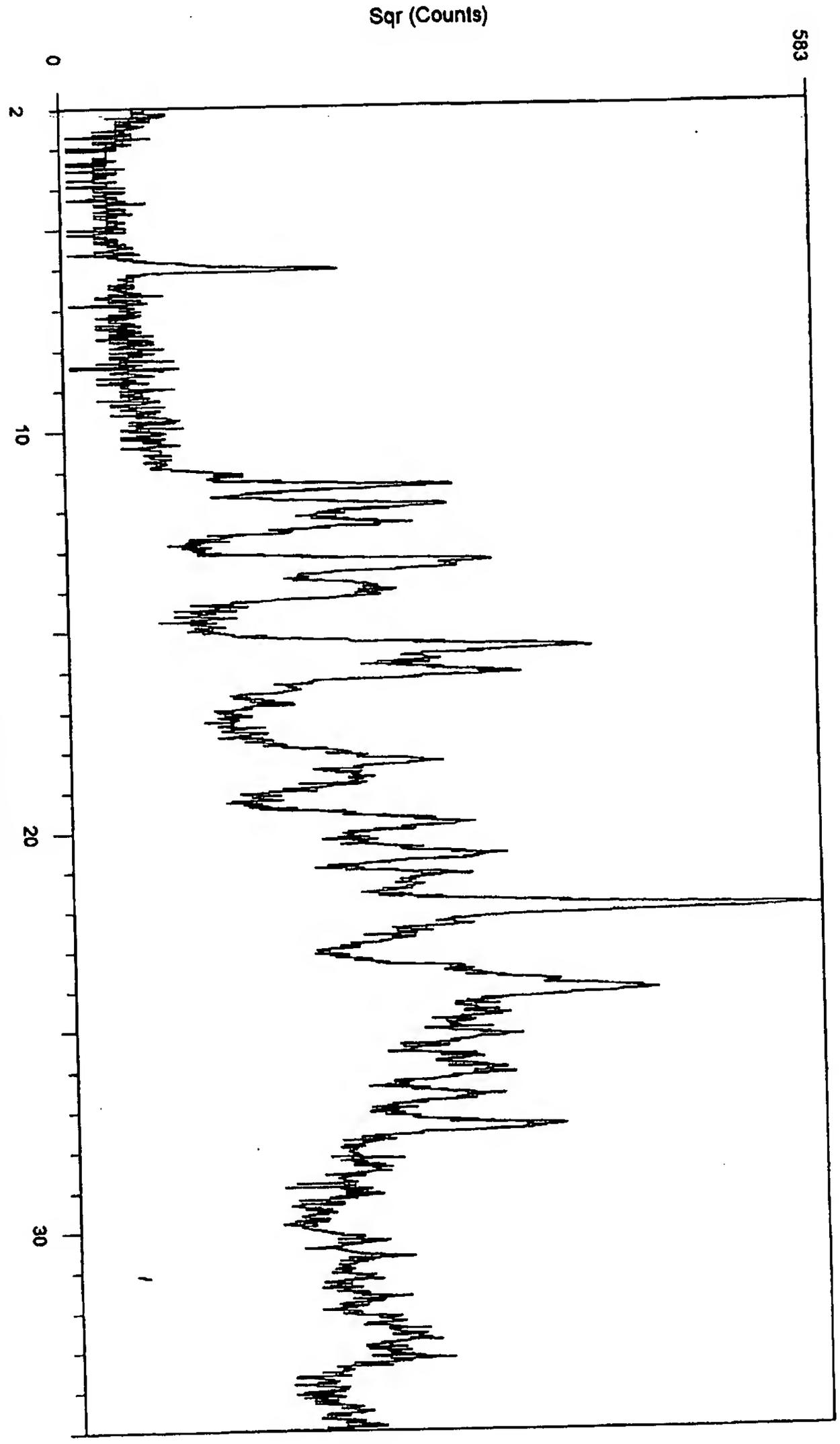
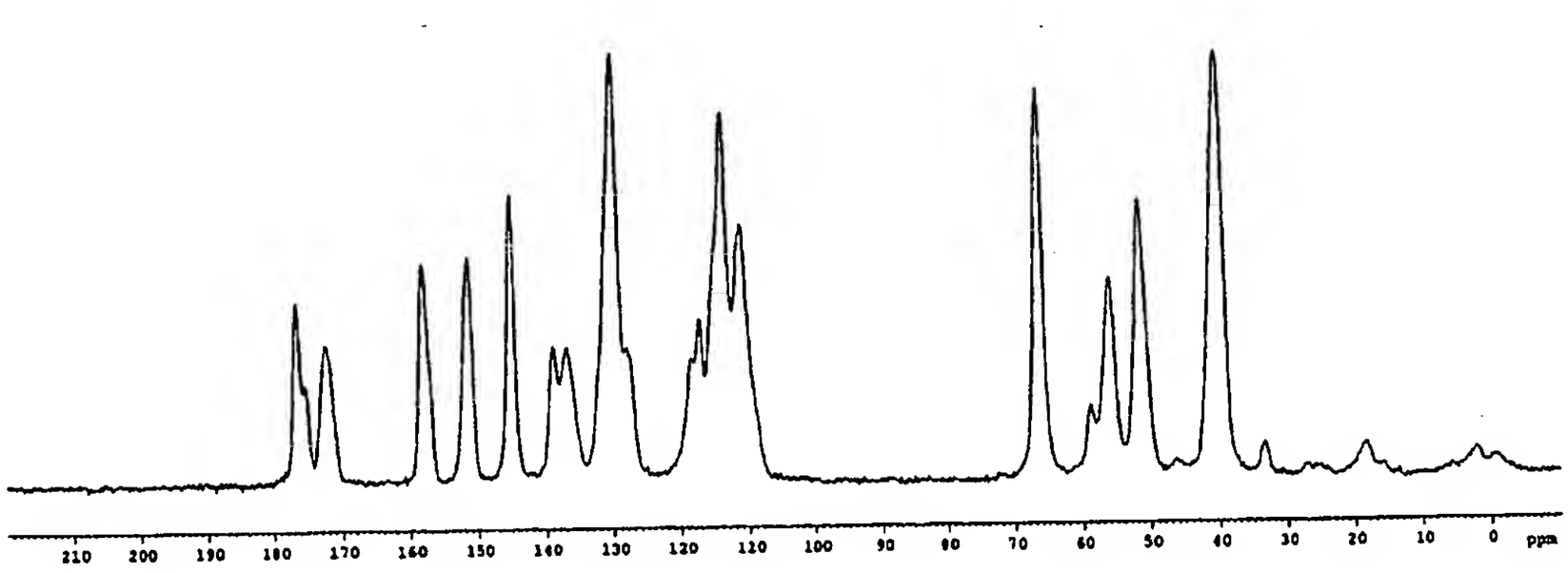


Figure 4 Solid State ^{13}C NMR spectrum of the Sulfate



INTERNATIONAL SEARCH REPORT

PCT/GB 02/05674

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/4439 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 05659 A (SMITHKLINE BEECHAM PLC; POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 (1994-03-17) cited in the application page 2, line 7 - line 14; claims 1,6,9-13	1,15, 18-21
Y	page 2, line 7 - line 14; claims	1-21
Y	WO 01 12628 A (BUCKINGHAM ROBIN EDWIN; SMITHKLINE BEECHAM PLC (GB); URQUHART MICH) 22 February 2001 (2001-02-22) page 1, line 31 -page 2, line 7 page 3, line 18 - line 22; claims 1,8-11	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2003	16/04/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Hass, C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	BERGE S M ET AL: "PHARMACEUTICALS SALTS" JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON, US, vol. 66, no. 1, 1977, pages 1-19, XP000562636 ISSN: 0022-3549 table I	1
A	WO 98 55122 A (PRICE ROBIN; SMITHKLINE BEECHAM PLC (GB); GRANETT JEFFREY ROGER (U) 10 December 1998 (1998-12-10) cited in the application page 8, line 1 - line 14; claims	1-21
A	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application claims 1,1,14-17; example 30	1,15-21

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/GB 02/05674

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 21 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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